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EXAMINER
KWON, BRIAN YONG S

ART UNIT	PAPER NUMBER
1614	10

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/835,099	BAMDAD ET AL.	
	Examiner	Art Unit	
	Brian S Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-123* is/are pending in the application.

4a) Of the above claim(s) *11-14,20,21,24-104,106-115 and 117-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,15-19,22,23,105 and 116* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's Response to Election/Restriction Requirement Acknowledged

1. Applicants election with traverse the Group I(f), claims 1-23 and 105-123, along with physostigmine as the elected species, is acknowledged. Applicants traverse the restriction requirement on the grounds that there would be no burden in searching the entire groups. This argument is not persuasive, as claimed invention would be distinctive, each from the other for the reason of the record. Furthermore, the search of the entire groups in the non-patent literature (a significant part of a through examination) would be burdensome.

It appears that applicants erroneously determine that claims 1-2, 8, 11, 14, 17-19, 22, 105 and 116 are readable on the elected species. However, the examiner finds that claims 1-10, 15-19, 22-23, 105 and 116 actually readable on the elected species.

With respect to applicants remarks regarding "the Examiner's description of this group does not precisely match the language of independent claims 1, 22, and 105 of the group, and it is understood that the scope of these claims will be defined by their language and equivalents", the applicants are correct. The examiner purposely placed independent claims 1, 22 and 105 together in the same group since search and examination on claims 1, 22 and 105 would not place an undue burden on the examiner (since all the independent claims 1, 22 and 105 are basically drawn to the same invention despite of slight difference in wordings). Should applicant disagree with the examiner that each independent claims are patently distinct, applicant should clearly admit on the record that this is the case. In that case, the instant claims are subjected to further restriction.

Therefore, the requirement is still deemed proper, and made Final. Claims 11-14, 20-21, 24-104, 106-115 and 117-123 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims, the requirement having been traversed in Paper No. 8.

Priority

2. Acknowledgment is made of a claim for domestic priority under 35 USC 119(e) (to a provisional application).

Claim Objection

3. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 1 relates to an administration of a composition comprising a compound represented by benzene ring structure (wherein benzene ring is substituted with R and R2), piperidine structure, pyridine structure and five member ring structures. However, the composition of claim 2 relates to an aromatic ring. Apparently, the scope of dependent claim 2 appears to be broader than parent claim 1, failing to further limit the subject matter of a previous claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10, 15-19, 22-23, 105 and 116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of a patient exhibiting the specific symptoms of Alzhimer's Disease (e.g., dementia) or treatment of Alzhimer's Disease associated with beta-amyloid peptide aggregate or fibril formations with the specific composition (i.e., physostigmine, atenolol, pindolol, etc.:.), does not reasonably provide enablement for (i) the claimed prophylactic use of said composition; (ii) the scope of treating all conditions or symptoms that are related to aggregate-forming species, aggregate formation or fibril formation (i.e., Familial British Dimentia, Parkinson's Disease, Finnish-type Familial Amyloidoses, Huntington's Disease, Frontotemporal Dementia, Senile Systemic Amyloidosis, Familial Amyloidosis, Transmissible Spongiform Encephalopathie, Gertsmann-Strausseler-Scheinker Syndrome, Fatal Familial Insomnia, Huntington's chorea, Kuru, Familial amyloid polyneruopathy, Creutzfeldt Jakob, Scrapie, bovine Sponfiorm Encephalopathy, multiple myeloma, Waldenstroms Macroglobulinemia, blockage of affected blood vessels caused by precitpiates of cryoglobulins, disseminated intrvascular coagulation, Glanzmann's thrombasthenia, Abnormal fibronectin aggregation, Sickle cell anemia, stroke and Type II Daibetes); (iii) the scope of all the species of the genus represented by the claimed structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With respect to "the claimed prophylactic use of said composition",

Although the claims have been presented with languages "treating a human susceptible to..." (claim 1); "promoting the prevention..." (claim 22); and "treating a subject at risk of developing a disease...", the scope of the claims read on the prophylactic use of the claimed composition since the claims require the administration of the claimed composition prior to onset of the diseases or symptoms of the diseases.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: nature of the invention, breadth of the claims, state of the art, guidance of the specification, predictability if the art, and the working examples. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to the methods of treating or preventing conditions caused by aggregate forming species, aggregate or fibril formation in subjects with the administration of the instant composition. The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders and subsequently administering the instant composition.

Breadth of Claims: The complex nature of the claims is exacerbated by the breadth of the claims. The claim encompasses prevention of complex disorders that may have potential causes other than those disclosed in the specification. This may or may not be addressed by the administration of the composition. Moreover, the specification is directed to various neurodegenerative diseases or non-neurodegenerative diseases due to conditions relating to

where the aggregate-forming species, aggregates or fibril formations are manifested (i.e., Alzheimer's Disease and Disseminated Intravascular Coagulation).

State of the Art: The state of the art does not recognize the administration of compositions to prevent the disorders as required in the instant claims. The state of the art recognizes the treatment of the symptoms of the specific disorders but not their cure. See also applicant's admission on the state of the art (page 3, lines 25-28).

Guidance of the Specification: The guidance given by the specification on how to prevent the disorders is absent. Guidance for treatment of Alzheimer's Disease by inhibiting conversion of β-amyloid protein to the fibrillar beta-sheet form (page 47, line 19 thru page 52, line 29) is provided, however, no evidence that these conditions are prevented is provided.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to completely preventing conditions caused by aggregate-forming species, aggregates or fibrils formation (e.g., Alzheimer's Disease, Parkinson's Disease, etc...) in mammals with the administration of the instant composition makes practicing the claimed invention unpredictable in terms of the prevention of the disease.

The Amount of Experimentation Necessary: The art demonstrates treatment of the specific diseases or conditions caused by the specific aggregates or fibrils formation, but does not teach elimination (prevention) of these conditions. Therefore, the practitioner would turn to trial and error experimentation to make/use the instant compositions for preventing memory disorders, hyperglycemia, or skin infections in mammals, without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

For examination purposes, the phrase "treating a human patient susceptible...symptoms of conditions" in claim 1, "promoting the prevention...a disease" in claim 22 and "treating a subject at risk of developing a disease" are interpreted as the treatment of the instant conditions.

With respect to "the scope of treating all conditions or symptoms that are related to aggregate-forming species, aggregate formation or fibril formation" and "the scope of all the species of the genus represented by the claimed structure",

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: nature of the invention, breadth of the claims, state of the art, guidance of the specification, predictability if the art, and the working examples. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to the methods of treating symptoms of diseases or treating diseases that are related to aggregate-forming species, aggregate formation or fibril formation in subjects with the administration of the instant composition represented by the claimed structures (except claim 116). The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and subsequently administering the instant composition.

Breadth of Claims: The claims are very broad. Independent claims 1, 22 and 105 encompass any diseases or symptoms that are related to aggregate-forming species, aggregate formation or fibril formation or any species that fall under the definition of the generic structures. The limiting claims that limit the disease still claim various disease state, neurodegenerative

diseases and non-nuerodegenerative disease. Exception to claim 116, the limiting claims still read on the broad claimed structures.

State of the Art: The state of the art does not recognize the administration of any compositions of the genus to treat all diseases or symptoms of all diseases that are related to aggregate-forming species, aggregate formation or fibril formation.

Guidance of the Specification: The specification (page 47, line 19 thru page 52, line 29) filed April 12, 2001 discloses an in vitro study (in drug screening method) for determining effectiveness of a candidate drug in inhibiting beta-amyloid peptide (e.g., Aβ1-42 and Aβ 1-40) aggregate formation or amyloid precursor protein (APP) production, secretion, or cleavage and thus affect beta-amyloid peptide aggregate formation. The specification provides no guidance, in the way written description, the claimed composition is effective in inhibiting non-beta-amyloid peptide aggregate formation (non-Aβ peptide) or non-APP production, secretion or cleavage in such a manner as to have a positive therapeutic effect useful for the treatment of all neurogenerative diseases or non-neurodegenerative diseases (recited in claims 7 and 10).

The specification discloses examples of compositions that inhibit beta-amyloid peptide aggregate formation and/or "pre-formed aggregate" such as atenolol, pindolol, 4-aminopyridine, physostigmine, cimetidine, supiride, oxotremorine methiodide, uracil, 5-trifluoromethyl-5,6-dihydro, alpha-methyl norepinephrine, isoproterenol, and others (page 23, line 6 thru page 25, line 26). Further, the specification relates examples of compositions to the generic structures (genus) having di-substituted aromatic rings, pyridine derivatives, piperidine derivatives, a five membered ring including at least one heteroatom, at least two rings bridged by at least one atom, at least two rings bonded directly to each other, a ring containing at lest one carbonyl and an

alkyl chain (page 15, line 27 thru page 23, line 5). It appears that various examples of compositions disclosed in the specification (page 23, line 6 thru page 25, line 26) are known to be well-known compositions that inhibit beta-amyloid peptide aggregate formation and/or "pre-formed aggregate" prior to the applicants invention. Although the specification correlates the specific composition to the generic structure, the specification provides inadequate information regarding whether the species of the genus other than disclosed examples in the specification would have similar properties and, thus, the same use as the genus as a whole. Although the specification discloses a screening assay (in vitro) for determining effectiveness of a candidate drug in inhibiting beta-amyloid peptide aggregate formation or amyloid precursor protein (APP) production, secretion, or cleavage and thus affect beta-amyloid peptide aggregate formation, the conclusion of the species of the genus as having similar properties as the genus as a whole requires undue amount of experimentation. This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosrue should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re

Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the treatment of various neurodegenerative diseases or non-neurodegenerative diseases due to conditions where the aggregate-forming species, aggregates or fibril formations are manifested and where the different type of proteins or polypeptides are involved in the formation of aggregates, fibrils or aggregate-forming species (i.e., Alzheimer's Disease and Disseminated Intravascular Coagulation) in mammals with the administration of the instant composition makes practicing the claimed invention highly unpredictable.

The Amount of Experimentation Necessary: The art demonstrates the reduction of the specific Alzheimer's symptom, for example dementia, thereby treating Alzheimer's Disease but does not teach whether (i) beta-amyloid aggregates are definite causative factor for the symptoms of Alzheimer's Disease or other neurodegenerative diseases (e.g., Parkinson's Disease, Finnish-type Familial Amyloidoses, etc...); (ii) the reduction of beta-amyloid aggregates or fibril formation can treat all symptoms of neurodegenerative or non-neurodegenerative diseases; (iii) the reduction of beta-amyloid aggregates or fibril formation could predict the positive treatment outcome of Alzheimer's Disease or other neurodegenerative or non-neurodegenerative diseases; (iv) the effective agent in inhibiting the conversion of beta-amyloid protein to fibrillar beta-sheet form or reducing APP production, secretion or cleavage is going to work similarly in inhibiting or reducing other types of proteins or polypetides which share no sequence homology or even conserved motif; (v) all the claimed conditions characterized by "aggregate-forming species", " aggregate formations" or "fibril formations" can

be treated by the claimed composition effective in reducing beta-amyloid aggregates and APP production, secretion or cleavage. Therefore, the practitioner would turn to trial and error experimentation to make/use the instant compositions for treating "symptoms of conditions characterized by aggregate-forming species", "a disease caused by aggregate formation" and a patient having "a disease associated with fibril formation" , without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-2 and 3-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite by reciting "symptoms of conditions characterized by aggregate-forming species associated with a disease" and "the patient being otherwise free of indication for treatment with the composition".

The specification (page 10, line 29 thru page 11, line 1) defines that "Aggregate-forming species" refers to "biological species associated with disease or non-disease process involving aggregates, as defined above, having sufficient binding capacity to bind to other molecules associated with the disease or non-disease process (including like molecules), to form fibrils or aggregates characteristic of the process". Further, the specification discloses that the meaning of "aggregate forming species" would be apparent to those ordinary skill in the art as it is applied to

neurodegenerative disease aggregate-forming species, non-neurodegenerative disease aggregate-forming species, and non-disease aggregate-forming species" (page 10, lines 10-13). Unlike applicants assertion, "aggregate forming species" is not relatively well recognized in the art (based on the examiner's independent search). It is not clear at all what is meant by "biological species associated with disease or non-disease process involving aggregates, as defined above, having sufficient binding capacity to bind to other molecules associated with the disease or non-disease process (including like molecules), to form fibrils or aggregates characteristic of the process". It is noted to applicants that wording of a claim or specification should provide reasonable clarity to the ordinary skill in the art.

In addition, claim 1 recites the limitation where the patient is "free of indication for treatment with the composition". Reading claim 1 in whole context (and in view of the specification), it is not clear at all what is meant by "the patient being otherwise free of indication for treatment with the composition". Since part of the claim 1 can be interpreted as the treatment method where the patient is "exhibiting symptoms of conditions", it is vague and unclear of in what situation the patient is "being otherwise free of indication for treatment with composition". For the purpose of the examination, such limitation are considered as non-limiting feature of the invention.

Furthermore, claim 7 recites the abbreviation such as "AD" in line 3. It is not clear what refers to "AD" since no support can be found for the meaning of such abbreviation in the specification. Does it refer to Alzheimer's Disease? If it does refer to Alzheimer's Disease, claim 7 is presented with redundant words, Alzheimer's Disease in line 2 and "AD" in line 3.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-2, 4-8, 17-19, 22-23, 105 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by Asthana et al. (Clinical Pharmacology and Therapeutics, 1995, 58(3), 299-309).

Asthana teaches the use of physostigmine as a cholinesterase inhibitor for treating patients with Alzheimer's disease by improving the cognitive dysfunction (abstract).

Although the reference is silent about (i) "the composition is capable of crossing the blood/brain barrier" (as required in claim 8); (ii) "the composition demonstrates...from soluble, monomeric state to an insoluble..." (as required in claim 17); (iii) "the composition demonstrates...from a α-helix to a insoluble..." (as required in claim 18); and (iv) "the composition demonstrates...from a soluble, monomeric state to an early intermediate aggregate" (as required in claim 19), such feature or property is deemed to be inherent to the referenced physostigmine. Therefore, the reference anticipates the claimed invention.

Conclusion

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (703)308-5377. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax number for this Group is (703) 308-4556.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brian Kwon

[illegible] KRASS
PRIMARY EXAMINER
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